ORIGINAL ARTICLE

Modelling complex mixtures in epidemiologic analysis: additive versus relative measures for differential effectiveness

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ABSTRACT

Objectives Mixed exposures are often combined into single exposure measures using weighting factors. This occurs for many complex mixtures in environmental and occupational epidemiology including multiple congeners, air pollutants and unique forms of ionising radiation, among others.

Methods The weights used for combining exposures are most often determined from experimental animal and cellular research. However, evidence from observational research is necessary to support their use in risk analyses, since results from experimental research do not directly translate to observational epidemiology.

Results Using simulated data, we show that ratio-based relative weights cannot be reliably estimated from observational research. As a solution to this problem, we propose an approach for estimating differences in effectiveness of distinct exposures based on their *excess* effectiveness compared with a reference exposure.

Conclusions This alternative is easy to calculate and provides reliable estimates of differences in effectiveness of distinct exposures. This is important to regulatory bodies using relative measures for policy decisions, as well as practicing epidemiologists conducting risk analyses.

INTRODUCTION

Epidemiologists often investigate the effects of a potentially complex mixture of exposures. Recently, the National Institute of Environmental Health Sciences labelled the evaluation of complex mixtures a priority issue.[1] Additionally, a recent workshop of the US Environmental Protection Agency called for further development of methods to evaluate single pollutants within models considering multiple pollutants.[2]

In some cases, distinct exposures or agents are combined together into a single metric of aggregated exposure. One reason why this is done is to reduce problems of estimation arising from high correlation between measures of exposure to various constituents of the mixture. Another rationale is that components of a mixture with similar chemical structure may act on the same disease pathway.[3] In addition, the effects of rare exposures can be difficult to estimate; the contribution to disease risk of rare exposures may be able to be accounted for through aggregation with other, similarly damaging exposures.

What this paper adds

► Ratio-based relative weights are often used to combine complex mixtures, but with little or no support from observational epidemiology; however, these weights are not easily obtained from observational epidemiology.

► This study explains and demonstrates why ratio-based relative weights are problematic, and provides an easy alternative based on excess measures of differential effectiveness for complex mixtures.

► Policy makers and researchers conducting risk assessment can use our proposed alternative for better evaluation of the differential effects of a complex mixture of exposures.

In order to combine different types of exposures into a summary metric, a weighting factor is often applied to each type of exposure reflecting an assumption regarding its relative effectiveness at causing the health outcome under investigation. Examples include the effects of unique forms of ionising radiation, multiple air pollutants and different PCB congeners,[4 5] among others. Choice of such weights often follows from cellular and animal research[6 7]; however, different studies may suggest different values for weights, and extrapolation to human health effects is often uncertain. Thus, it is important to empirically evaluate decisions regarding choice of weights used in epidemiologic analyses.

When estimated in epidemiologic studies, these weights are often calculated as the ratio of the slope coefficients of two exposures modelled independently or in a single regression model. In this paper, we explain and demonstrate why estimation of relative weights from observational data as commonly practiced is inherently problematic. We propose an alternative metric to estimate the effectiveness of one exposure compared with another in settings in which a population is exposed to a mixture of two or more types of exposures as excess versus ratio-based effectiveness. Through simulated data we illustrate that our proposed approach yields valid estimates of differences in the effectiveness of exposures. Our method can be easily applied to complex mixtures across environmental and occupational epidemiology.

Methodology

METHODS

Consider a model for the relationship between two exposures and outcome of the form,

$$\text{Rate} = e^{\theta i}[1+(\beta_1 \times X + \beta_2 \times Y)] \qquad (1)$$

where $e^{\theta i}$ indexes the baseline rate in stratum i, X and Y represent two exposures of interest, often cumulative over some time period, with β_1 and β_2 representing the excess relative rate of the outcome per unit increase in X and Y, respectively. We will refer to this as the 'independent' model. Examples of exposures might include multiple congeners, pesticides, or distinct forms of radiation. X and Y may be combined into a single weighted exposure term, D, with weights determined by the relative effectiveness of one type of exposure over another. Supposing Y is the reference exposure, D is expressed as $D = q \times X + Y$, where q represents a fixed weight meant to reflect the relationship of X to an outcome of interest compared to Y's relationship to that same outcome, calculated from equation 1 as β_1/β_2.

If we wish to directly parameterise and, thus, estimate a relative weight from an observational study, we might consider a model, such as

$$\text{Rate} = e^{\theta i}[1+\gamma(\tau \times X + Y)] \qquad (2)$$

where τ is the effect of X relative to Y. The parameter τ is typically distinguished from q in the toxicology literature because the former is a quantity estimated from the model and data. Note that equation (2) is a simple reparameterisation of equation (1) that allows direct estimation of a relative weight; exposures X and Y are combined into a single exposure given the weight, τ. Since τ is estimated from the model and data, as $\hat{\tau}$, we obtain a SE for its estimated value which we could also calculate from equation 1. Unfortunately, $\hat{\tau}$ as estimated from these models, may not have desirable statistical properties.

The term τ is calculated as the ratio of estimates for the effect of X and Y. When β_1 and β_2 are estimated using standard frequentist techniques, their estimates, $\hat{\beta}_1$ and $\hat{\beta}_2$, are assumed to have normally distributed errors. This has consequences for estimation of τ since the ratio of two normally distributed estimators follows a non-central Cauchy distribution.[8] The Cauchy distribution is similar to a normal distribution but with longer, fatter tails and an extreme peak at its mode. The notable aspect of a Cauchy distribution is that it lacks a mean or SD.[9] Since the mean and SD are undefined, attempts to estimate these parameters will typically result in poorly functioning procedures with no guarantee that we will be estimating the parameter of interest, or that our Wald-type CIs will have nominal coverage. From a substantive perspective, the non-central Cauchy formed by the ratio of these normal random variables can be either unimodal or multimodal.[8] A bimodal distribution for the effect of interest may not be substantively appealing. However, we suggest below that a multimodal distribution for $\hat{\tau}$ would not be uncommon.

An alternative to assessing effects of exposure on a ratio scale is to focus on a model that allows one to evaluate absolute difference in the effect of two or more exposures. Consider equation 3,

$$\text{Rate} = e^{\theta i}(1+\beta(X+Y)+\omega \times X) \qquad (3)$$

where ω represents the *excess* biological effectiveness of some outcome for exposure X compared to exposure Y, or $\beta_1-\beta_2$ from equation 1. We will refer to this as the excess effectiveness

model. Again, we are reparameterising equation 1 to allow estimation of the effectiveness of one exposure compared with another. Here, X and Y are summed, and any difference between the effectiveness of X relative to Y is described by ω. Similar to τ in equation 2, this model allows direct estimation of a value for the excess effectiveness (which would be identical to the difference of $\beta_1-\beta_2$ from equation 1) as well as its variance, which would require additional calculations if equation 1 were estimated. By contrast with equation 2, the estimate of ω, $\hat{\omega}$, will be asymptotically normally distributed instead of Cauchy distributed. While both terms can be estimated from epidemiologic data when people are exposed to a mixture of two or more types of hazards, the excess measure provides a more statistically reliable metric for integrating differential effects of exposure and is simple to apply. It should be noted that the exposures of interest should always be measured in the same units; for example, X and Y could be two forms of radiation measured in units of absorbed dose (mGy). This is necessary for calculation of weights for all the equations described above. Below, we present an example where the quantities of interest are $\hat{\tau}$ and $\hat{\omega}$.

Simulation example

Simulations were based on a method developed by Richardson and Loomis.[10] Cohort sizes of 5000, 10 000 and 20 000 workers were simulated to increase the precision of the estimated baseline exposure effect (more workers will result in greater precision) and investigate how this influenced the estimation of the τ and ω. For each simulation, 500 cohorts were simulated, and for each cohort, we randomly assigned values for age at first exposure (18 years plus a random exponential variable with mean 10) and maximum follow-up time (40 years minus a random exponential variable with mean 5) to each worker. Also, each worker was assigned a maximum exposure duration of 15 years and intensity (exposure per year) to two exposures, x and y. Exposure intensity variables are distributed with $x \sim$ lognormal ($\mu_x=0$, $\sigma_x=0.5$) and $y \sim$ lognormal ($\mu_y=0$, $\sigma_y=1$), both truncated to be between >0 and <10. We conducted simulations where x and y are assumed to be independent, and where we induced correlation between the two (r=0.5).

From start of follow-up until each year, the worker's current age and cumulative exposure (equal to the intensity of the worker's exposure multiplied by exposure duration) was calculated. Also, at each year, the mortality rate for the outcome of interest (conditional on survival to that age) was assigned to each worker such that:

$$\text{Rate} = e^{-7.2+1.5 \times \ln\left(\frac{\text{age}}{55}\right)}(1+0.01 \times Y_{cumexp}+0.04 \times X_{cumexp})$$

where Y_{cumexp} and X_{cumexp} represent the sum of exposures y and x, respectively, from the start of follow-up to each subsequent year. This model form is the same as that identified in equation 1; however, we reiterate that we could generate the same data using equations 2 and 3. The same simulated data will be used to fit models for equations 1–3. We should note that while X and Y denote a time-varying measure of cumulative exposure here they could represent any summary metric of exposure (such as a time window or single point exposure). Additionally, at each year, a conditional probability, c, of mortality from any other outcome (conditional on survival to that age)

was assigned to each worker based only on the worker's age using the following formula:

$$c = e^{-5 + 5 \times \ln\left(\frac{age}{55}\right)}$$

Two Bernoulli random variables were assigned to each worker at each year, one with probability h, and one with probability c. A Bernoulli random variable of 1 represents a death in that year from the outcome of interest or from another outcome, respectively. A worker is followed-up until death. A worker is considered censored if simulated death is from another outcome, or if he made it through all years of his maximum follow-up time with no deaths. A worker is considered a case if death is from the outcome of interest. The final cohorts consisted of 5000, 10 000, or 20 000 workers with variables indicating for each worker the age at first exposure, age at death/censor, age at last exposure (which is the minimum of age at first exposure plus 15, and age at death/censor), exposure intensity per year, and case status. Results fit using equation 1 are presented in order to assess the change in the stability of parameter estimates as we increase the number of simulated cohorts, and to display alternative calculation of CI coverage of τ using the delta method. We fit models applying equations (2) and (3) to the data in order to empirically estimate τ and ω, respectively. The true values of β_1 (effect of exposure X) and β_2 (effect of exposure Y) are 0.04 and 0.01, respectively. Thus, the true τ and ω are $0.04/0.01 = 4$ and $0.04 - 0.01 = 0.03$, respectively. This value is within the range of expected values for some forms of radiation[6 11 12] as well as multiple congeners.[4 5] For each simulated dataset, we saved $\hat{\tau}$, $\hat{\omega}$ and their empirical and estimated SEs. *Empirical* SE is calculated as the SD of the 500 simulated parameter estimates. The *estimated* SE represents the average of the SEs calculated for each individual simulation. We also calculated whether estimated CIs contained the true value of the parameters of interest. We use profile likelihood ratio-based methods to calculate CIs and coverage probability since Wald-based methods are known to perform poorly for linear rate models.[13 14] Simulations were conducted using SAS Software (V.9.1.3, SAS Institute, Cary, North Carolina, USA)

and analyses were conducted using the procedure NLMIXED in that statistical package. Additionally, analyses were conducted where the number of simulated cohorts was increased from 500 to 10 000. However, these results were similar to those presented and, thus, are not shown. The online supplementary eAppendix provides code for implementing these models with the procedure NLMIXED in SAS.

RESULTS

Table 1 summarises results of the simulations. The independent model (equation 1) returns similar estimates for $\hat{\beta}_1$ and $\hat{\beta}_2$ for simulations of 5000–20 000 workers. As the number of workers increases, the empirical and estimated SEs decrease. These estimates are similar for the independent model, so here we discuss the empirical SE. For simulations including 5000, 10 000 and 20 000 workers, the empirical SEs for $\hat{\beta}_1$ are 0.0253, 0.0146 and 0.0100, respectively; errors for $\hat{\beta}_2$ are similar to $\hat{\beta}_1$ and follow the same pattern of decrease with increasing number of workers. Finally, 95% CI coverage is close to the nominal level for all parameters and simulations.
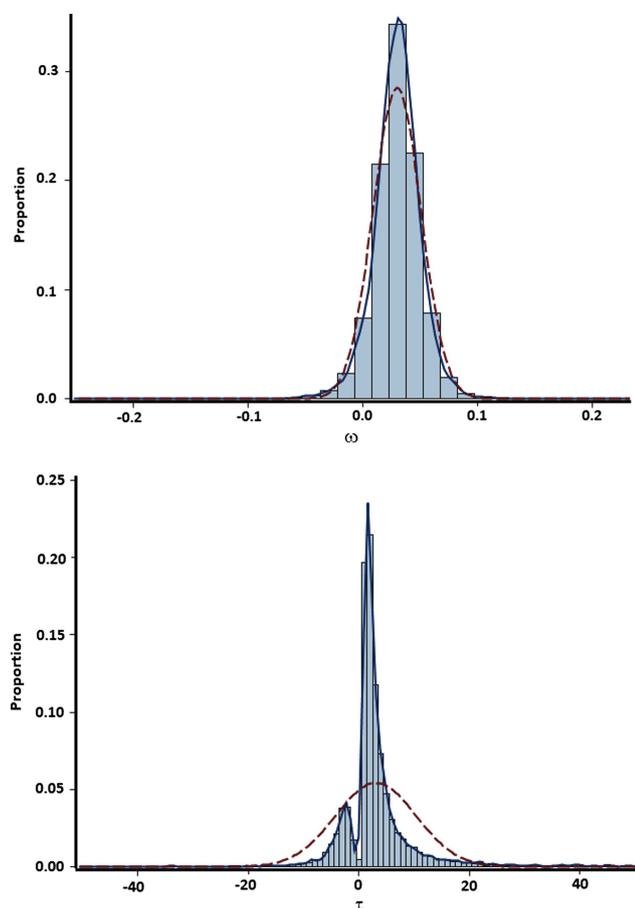
Results for $\hat{\gamma}$ from equation 2 follow those for the independent model; that is, they improve as the number of observations increases. However, the estimate of $\hat{\tau}$ is unstable. The model fails to provide an unbiased estimate of the true value of 4.0 in these simulations. Further, the estimated SEs overestimate the empirical SEs and do not always decrease when increasing the number of workers. This suggests that estimates of SEs will be too large, on average, in a given study. Likelihood-based CIs for τ give approximately correct coverage in all simulations. This may be due to the combination of a biased estimator with CIs that are too wide. Finally, only 87–90% of the 500 simulations for τ were able to converge, suggesting inherent difficulty in estimating a ratio measure of effectiveness. This may explain some of the bias observed in the results.

The excess effectiveness model (equation 3) displays behaviour similar to the independent model (equation 1). The simulation of 5000 workers returns the expected point estimate ($\hat{\omega} = 0.031$) and provides appropriate CI coverage; these results are consistent when increasing the number of workers.

Table 1 Simulation results comparing equations 1–3 with varying numbers of simulated workers

Equation	Number of workers	Number of cohorts	Parameter estimated	Mean of estimated parameter	Empirical SE	Estimated SE	Likelihood 95% CI coverage
1	5000	500	$\hat{\beta}_1$	0.0150	0.0253	0.0235	95.8
			$\hat{\beta}_2$	0.0459	0.0251	0.0223	94.2
2		434	$\hat{\gamma}$	0.0178	0.0260	0.0248	95.2
			$\hat{\tau}$	2.854	6.725	14.63	94.7
3		500	$\hat{\beta}$	0.0150	0.0253	0.0235	95.8
			$\hat{\omega}$	0.0309	0.0200	0.0201	95.6
1	10 000	500	$\hat{\beta}_1$	0.0116	0.0146	0.0141	95.6
			$\hat{\beta}_2$	0.0418	0.0133	0.0130	94.8
2		434	$\hat{\gamma}$	0.0138	0.0144	0.0144	94.9
			$\hat{\tau}$	4.632	8.811	15.11	94.7
3		500	$\hat{\beta}$	0.0116	0.0146	0.0141	95.6
			$\hat{\omega}$	0.0302	0.0136	0.0129	93.6
1	20 000	500	$\hat{\beta}_1$	0.0109	0.0100	0.0096	94.4
			$\hat{\beta}_2$	0.0410	0.0088	0.0089	95.4
2		451	$\hat{\gamma}$	0.0125	0.0094	0.0097	95.3
			$\hat{\tau}$	5.296	6.668	9.712	94.2
3		500	$\hat{\beta}$	0.0109	0.0100	0.0096	94.4
			$\hat{\omega}$	0.0300	0.0090	0.0088	94.4

Methodology

Figure 1 Distribution of relative weight (bottom) and excess weight (top) values from 10 000 simulated cohorts of 5000 workers. Access the article online to view this figure in colour.

Table 2 $\hat{\tau}$ Calculated from equation 1 with the delta method for 500 cohorts

Number of workers	Mean of estimated parameter	Empirical SE	Estimated SE	Wald 95% CI coverage
5000	0.5741	21.25	145.8	72.6
10 000	−0.3110	149.9	537.4	81.2
20 000	7.543	45.73	412.8	84.8

those for which the model in equation 2 did not converge. Table 2 summarizes the results of applying the delta method to calculation of the relative effectiveness and its SE from $\hat{\beta}_1$ and $\hat{\beta}_2$ obtained from equation 1 for each simulation scenario presented in table 1. Increasing the number of workers from 5000 to 20 000 for 500 simulated cohorts provides some improvement of the 95% CI coverage, increasing from 72.6% to 84.8%. However, the empirical and estimated SEs are rather large for all simulations. None of these scenarios provide an unbiased estimate of $\hat{\tau}$. Finally, additional analyses were conducted that assessed the effect of introducing correlation (correlation coefficient=0.5) between X and Y; however, results were similar to those presented, and thus are not included.

DISCUSSION

The empirical evaluation of the differential effects of multiple exposures from epidemiological data is complicated by its reliance on calculating the ratio of two normally distributed parameters. Direct parameterisation (equation 2) as well as the calculation based on the ratio of two model parameters (equation 1) are unable to provide reliable estimation of a ratio measure of effectiveness. The result is an estimator that is likely to be biased, as demonstrated by our simulations. We propose an excess metric on the additive scale to directly estimate the differential effect of exposures as a simple alternative. We show that increasing the amount of data does not necessarily improve estimation of the relative effectiveness measure, τ. Additionally, we show that the excess measure, ω, will provide more precise and unbiased estimates of differential effects of unique exposures by taking the absolute difference of two parameters and providing a measure that also follows a normal distribution.

The use of fixed weights to combine multiple, unique exposures is common in the field of environmental and occupational epidemiology. In radiation epidemiology, the relative biological effectiveness (RBE) is used to specify a fixed weighting factor for combining different forms of radiation in a diverse mixture into a single exposure metric. When summing multiple congeners, researchers use a relative potency factor (RPF) or toxic equivalency factor (TEF), which is an estimate of an individual chemical's ability to cause a toxicologic or biologic outcome relative to 2,3,7,8-TCDD or PCB 126.[16][17] RPFs or TEFs are also used to combine distinct pesticides, particularly organophosphates and polycyclic aromatic hydrocarbons into a single exposure measure.[18][19] Evidence regarding RBE, TEF and RPF is often drawn from toxicology research so that the value can be implemented in risk assessment or epidemiologic analyses to create more parsimonious models.[4] This is likely necessary because a measure of relative effectiveness often cannot be reliably estimated from observational data.

If the RBE, RPF, or TEF correctly describes the relative effects of multiple exposures, and if the exposures can be summed assuming they work in a single disease pathway, then

Additionally, the empirical and estimated SEs decrease when we increase the number of simulated workers. These values are similar, so we only discuss the empirical SE here. The empirical SE for simulations of 5000, 10 000 and 20 000 workers for the excess effectiveness coefficient are 0.0200, 0.0136 and 0.0090, respectively. Thus, the excess model follows a predictable pattern, similar to the independent effects model.

Figure 1 provides a visual summary of simulated values of $\hat{\tau}$ and $\hat{\omega}$; 10 000 simulations were used to aid in development of graphics; increasing the number of simulations yields results similar to table 1, and are not presented here. The histogram and kernel density smoother show that the distribution of $\hat{\tau}$ is multimodal. While one mode is very peaked for a positive value, there is a second, less pronounced mode below zero. The bimodal shape of the distribution arises from the fact that the reference exposure has a small effect with a wide enough variance to allow its estimate to be negative in some simulations. The simulations in which the reference exposure is small but positive yield a large positive value of $\hat{\tau}$, while the simulations in which the reference exposure is small but negative yield a large negative value of $\hat{\tau}$. By contrast, the histogram for $\hat{\omega}$ appears approximately normally distributed, and the shape of the distribution is not impacted by changes in the sign of the referent exposure.

A common alternative approach to directly estimating $\hat{\tau}$, is to calculate the ratio $\hat{\beta}_1/\hat{\beta}_2$ from equation 1 and to estimate the SE of the estimator with the delta method.[15] This approach allows us to assess the performance of $\hat{\tau}$ in all simulated datasets, even

they provide a useful tool for combining different exposures. Correct knowledge of a weighting value would allow easy pooling of multiple exposures into a single metric, simplifying risk assessment and epidemiologic analyses. While toxicology provides guidance for assigning weighting factors, there is often variation in estimates of the value across animal and cellular-level outcomes. Additionally, extrapolating information from toxicology to epidemiology is inherently problematic.[20] In the case that the weighting factor is mis-specified, risk estimates may be distorted.

Some researchers have attempted to empirically estimate the RBE in radiation research.[11 21] Shimizu et al[22] estimated values of the neutron RBE of 52.0 for leukaemia, and 10.1 for other cancers among A-bomb survivors, relative to gamma radiation; both estimates were subject to significant statistical uncertainty. Kellerer et al[23] also evaluated the RBE among updated A-bomb survivor data, relying on the minimum deviance to evaluate the best value for the RBE. They concluded that an RBE value for a neutron dose of 100 provided the best model fit. The 95% confidence bounds for this estimate were 25–400. Uncertainty of this degree has led researchers to conclude that the RBE cannot be estimated from epidemiological data.[24] While this assessment is reasonable, the challenge has as much to do with limitations of epidemiological data as with the fact that the ratio measure of effectiveness are quantities that do not lend themselves to empirical evaluation. Our results show that increasing the amount of data would not help estimation of the RBE. For this reason, we believe the excess measure is an appealing alternative to the RBE.

It is important to note that we include only limited simulations. The parameter values chosen in our simulation are consistent with values seen in the literature regarding effects of radiation or multiple congeners on various outcomes of interest.[11 12 25] Exposures to radiation, multiple congeners, or other common exposures, are often associated with only modest increases in risk due to exposure.[26] The instability of the relative measure of effect (RBE, TEF, or RPF) is augmented when the referent category has low risk. Had the referent effect been larger (or the variability of the referent parameter estimate sufficiently reduced by increasing the sample size), the undesirable properties of τ may have been less apparent. However, we included simulations with 20 000 workers (observations) with complete exposure history and demographic information and still observed bias in estimates of τ.

We conducted simulations where modest correlation between the variables was included, and our results were the same. However, applying any of these models in the presence of more highly correlated variable may result in less precise estimates. Stabilising estimates using Bayesian techniques may help in these settings.[27] Additionally, our weights do not solve issues of measurement error that are common in environmental and occupational epidemiology. That is, if the exposures are incorrect, the estimated weights will be subject to bias in all the models presented. The extent of bias that would be expected in the presence of measurement error is beyond the scope of the simulations presented in this paper. Our simulations dealt with the common excess relative risk model. When other models, particularly linear ones, are chosen by the investigators, simple transformations may be available to circumvent these problems. Similarly, other approaches, such as non-parametric bootstrapping, may be helpful in some settings.

We note that the difficulty in estimating relative measures of effect has been mentioned before.[28] Similar problems are observed in the toxicology literature when measuring LD50,

and in the cost effectiveness literature when estimating cost effectiveness ratios.[29] As in those fields, the difficulty in interpreting τ is compounded by the ability of the effect of either type of exposure to be negative. In the event that both coefficients in equation (1) are negative, we would estimate a positive estimate of τ. In the event that only one coefficient is negative, we would estimate a negative τ which would not agree with the order of the relationship suggested by independent risk coefficients; in other words, a more damaging exposure's relative effectiveness measure might suggest it to be more protective.

Estimation of an excess term is clearly more feasible than estimation of a ratio term from epidemiological data. Results of simulation data show that our alternative parameterisation provides more reliable estimation compared to a model with a parameter for relative effectiveness (equation 2). Like the ratio measure model, the excess measure model is amenable to application of a fixed value for the differential effects of unique exposures when evidence strongly supports such a term. Thus, the excess measure model has the dual use of allowing for estimation and application of weights for differential effects of mixed exposure to estimate cumulative risk.

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